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None

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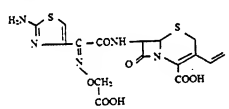
(54) Abstract Title
Cefixim preparation

(57) Cefixim of formula I is prepared by reacting an ester of formula II for 1.5 - 2 hours with an inorganic base in a mixture of dimethylformamide (DMF) and water, isolating the cefixim of required purity by acidifying the resulting reaction mixture and drying.



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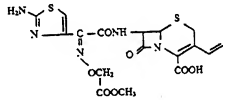

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DESCRIPTION

PROCESS FOR THE PREPARATION OF ORALLY ACTIVE CEPHALOSPORIN ANTIBIOTIC-CEFIXIM

This invention relates to a process for the preparation of orally active cephalosporin Antibiotic-Cefixim.

BACKGROUND

The first of a new series of cephalosporins which exhibit most of the properties desirable in a compount to be used for empiric therapy was Cefotaxime, a methoxy iminocephalosporin bearing a 2-iminotiazol-4-yl-group, which was swiftly followed by a number of very similar methoximes with different 3-substituents like Ceftizoxime, Cefmenoxime, Ceftriaxone and Ceftazidime compound **(Am.J.Med. (1985), Suppl 2A,14.; Am.J. Med.(1985,) Suppl 2A,21; Clin.Pharm.(1987),6,59.; Recent Advances in the Chemistry of β-Lactam Antibiotics, Special publication No. 52, The Royal Society of Chemistry, London, July 1984,p.1).**

Most of the aminothiazolyl cephalosporins are not absorbed from the GI tract and are not orall active. Cefixim is one such exception having carboxymethoxime group with small lipophillic 3-substituents. In the synthesis of Cefixim, 3-acetoxy group of 7-ACA is transformed via a 3-phosphonium salt and by Wittig reaction to a vinyl intermediate, which is then converted into Cefixim of formula I by standard procedure as described in **J.Antibiotics (1985), 38, 1738.** The said standard process comprises of the following steps:

- hydrolysis of methyl ester of formula II with inorganic base in aqueous

solution at 40 degree C for 7 hours.

- adjusting the pH of the resulting solution to 6.0 with 10% Hcl and subjecting it to column chromatography on Diaion HP-20 for purification;
- eluting the column with water and acidifying the fraction containing the desired compound (Cefixim) to pH 2.1 with 10% Hcl;
- stirring the resulting solution for one hour and collecting the precipitate of Cefixim by filtration.

The product yield in this process is 41%. This process suffers from the following drawbacks:

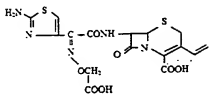
- The reaction is carried out at an elevated temperature, viz., 40 degree C and is completed in 7 hours. This leads to the formation of many undesirable impurities, and thereby decrease the purity of the final product in the solution.
- To get the desired purity of the final product, the said solution is subjected to column chromatography on Diaion HP -20 (Resin).
- The purification technique involve the use of column chromatography using Diaion HP-20 which is expensive and industrially uneconomical.

In US Patent 440924, Cefixim is obtained by hydrolysing tertiary butyl ester along with other protected substituents such as benzhydral and formamide by using trifluoroacetic acid. This process involves more number of complicated steps.

The obejcts of this invention are:

- To reduce the reaction time by increasing the speed of the reaction.
- To decrease the reaction temperature.
- To overcome the formation of undesirable impurities and increase the yield.

- To eliminate the use of expensive uneconomical purification technique and thereby decrease the production cost.
- To reduce the number of complicated steps in the process.



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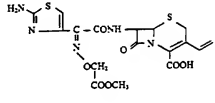

(II)

To achieve the aforesaid objectives this invention provides a process of preparing orally active cephalosporin antibiotic Cefixim of formula I comprising:

- reacting ester of formula II with inorganic base in a mixture of dimethyl formamide (DMF) and water at ambient temperature for a period of 1-1/2 to 2 hours;
- isolating Cefixim of required purity by acidifying the resulting reaction mixture and drying.

The ester of formula II preferably a methyl ester and inorganic base is preferably alkali carbonate. The ambient temperature during the reaction is preferably between 10 to 25 degree C. The DMF: water is in the ratio; 1:4 and the isolation of Cefixim is carried out by using 10% HCl.

In this method DMF not only acts as a solvent but also acts as a catalyst. It is well known that the lone pair of electrons at nitrogen atom of DMF coordinates and thus solvates the K^+ ion, thereby facilitating easy availability of CO_3^{2-} ions responsible for the hydrolysis of the ester group.

The invention will now be described with reference to the following examples:

EXAMPLES 1:-

To ester of formula II (500 mg, 1.07 mmol) in DMF was added K_2CO_3 (740 mg, 5.36 mmol) dissolved in water. Reaction mixture was stirred at 25 degree C. After the reaction was completed (2 hours as shown by HPLC monitoring), the product (Cefixim) was isolated by acidifying the reaction mixture to pH = 2.1 using 10% HC1. The resulting solid was collected by filtration and dried to afford 344 mg of the compound of formula I. Tests were conducted on this compound of formula I by standard methods and the results found were as follows:

Purity (HPLC) = 98.5%, $[\alpha]^{25}_{D}$ = -78.76°;

IR (Kbr) : 1770, 1668 cm^{-1};

^1H NMR (DMSO-d_6) : δ 3.54 -3.87 (2H, q, J = 17.61 Hz);

4.61 (2H, s) ; 5.21 (1H, d, J =4.81 Hz) ; 5.32 (1H, d, J = 11.37 Hz);

5.6 (1H, d, J =17.45 Hz) ; 5.81 (1H, dd, J = 4.81 Hz, 8.16 Hz);

6.81 (1H, s); 6.91 (1H, dd, J = 11.31 Hz, 17.51 Hz) ; 7.29 (2H, bs, D_2O exchangeable);

9.61 (1H, d, J = 8.2 Hz, D_2O exchangeable).

EXAMPLE 2:-

To ester formula II (500 mg, 1.07 mmol) in DMF was added Na_2CO_3 (583 mg, 5.5 mmol) dissolved in water. Reaction mixture was stirred at 25 degree C. After the reaction was completed (1 hr 50 min. as shown by HPLC monitoring), the product (Cefixim) was isolated by acidifying the reac-

tion mixture to pH - 2.1 using 10% HCl. The resulting solid was collected by filtration and dried to afford 305 mg of the compound of formula I. Tests were conducted on this compound of formula I by standard methods. The results found were as follows:

Purity (HPLC) = 97.3%, $[\alpha]^{25}{}_{D} = -77.92^{o}$;

IR (Kbr) : 1770, 1669 cm^{-1};

^{1}H NMR (DMSO-d_6) : δ 3.51 - 3.86 (2H, q, J = 17.58 Hz) ; 4.58 (2H,s) ; 5.20 (1H, d, J = 4.78 Hz) ; 5.31 (1H, d, J = 11.32 Hz); 5.6 (1H, d, J = 17.39 Hz); 5.81 (1H, dd, J = 4,78 Hz, 8.03 Hz); 6.81 (1H, s), 6.9 (1H, dd, J = 11.32 Hz, 17.41 Hz) ; 7.25 (2H, bs, D_2O exchangeable); 9.60 (1H, d, J = 8.11 Hz, D_2O exchangeable).

CLAIMS

1. A process of preparing orally active cephalosporin antibiotic-Cefixim of formula I comprising:

- reacting ester of formula II with inorganic base in a mixture of dimethylformamide (DMF) and water at ambient temperature for a period of 1-1/2 to 2 hours;

- isolating the Cefixim of required purity by acidifying the resulting reaction mixture and drying.

2. A process as claimed in claim 1 wherein the said ester of formula II is preferably methyl ester.

3. A process as claimed in claim 1 wherein the inorganic base is alkali carbonate.

4. A process as claimed in claim 3 wherein the alkali carbonate is Potassium/Sodium Carbonate.

5. A process as claimed in claim 1 whereim the DMF and water are in the ratio 1 : 4.

6. A process as claimed in claim 1 whereim the ambient temperature during the reaction is between 10-25 degree C.

7. A process as claimed in claim 1 whereim the acidification of the resulting reaction mixture for isolation of Cefixim is carried out by 10% HCl to pH 2.1.

8. A process as claimed in claim 1 substantially as hereinbefore described in Example 1 or Example 2.

9. An oral pharmaceutical composition comprising an orally active caphalosprin antibiotic-Cefixim when prepared by the process as claimed in any one of the preceding claims.

The Patent Office

INVESTOR IN PEOPLE

Application No: GB 9821966.0
Claims searched: 1-9

Examiner: Peter Davey
Date of search: 1 December 1998

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.P): C2C (CKE, CPK)

Int Cl (Ed.6): C07D 501/04

Other: Online: WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
	NONE	

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.